urational isomer. This clearly indicates that the experimentally determined conformational parameters measured for the minor component are better suited to the trans configurational isomer.

The average values and standard deviations of the torsions during the NOE-restrained simulations are given in Table I. The torsions listed for the cis and trans isomers are from the application of the NOEs measured for the major and minor components, respectively. There are only two positions in the ring system that show significant differences: The torsion between atoms C9 and C10 changes by 180° while the C17–C18 torsion swivels by approximately 60° to compensate. These changes are reflected in the differences of the ^{13}C chemical shifts of the carbons involved in these torsions.[12]

Outside of the macrocyclic system, the molecular dynamics simulations suggest that the orientation of the six-membered ring (atoms 29–34) is different in the cis and trans isomers. The torsions 24–25 and 25–26 project the six-membered ring in opposite directions with regard to the plane of the macrocycle. This difference is illustrated by the minimum-energy structures for the cis and trans conformers taken from the NOE-restrained molecular dynamics simulations (Figure 2).

The conformation of the cis isomer in solution is similar to the X-ray structure through most of the molecule (see Table I). There are significant differences at the torsions between atoms 21–22, 22–23, 23–24, 24–25, and 25–26. This produces an extended and relatively "flat" structure within the crystal with the six-membered ring projecting out in the plane of the macrocycle. This flat orientation likely arises from the packing forces within the crystal. The importance of the orientation of this exocyclic portion is currently being investigated.

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(12) The differences in the chemical shifts of the carbons between the two isomers (major to minor) are +4.65, +1.15, −3.54, +1.63, −0.94, and +2.53 ppm for carbons C6, C8, C9, C10, C11, and C16, respectively. There are only minor differences (<0.5 ppm) in the chemical shifts of the remaining carbons.

Synthetic Studies on Quassinoids: Total Synthesis of (±)-Chaparrinone

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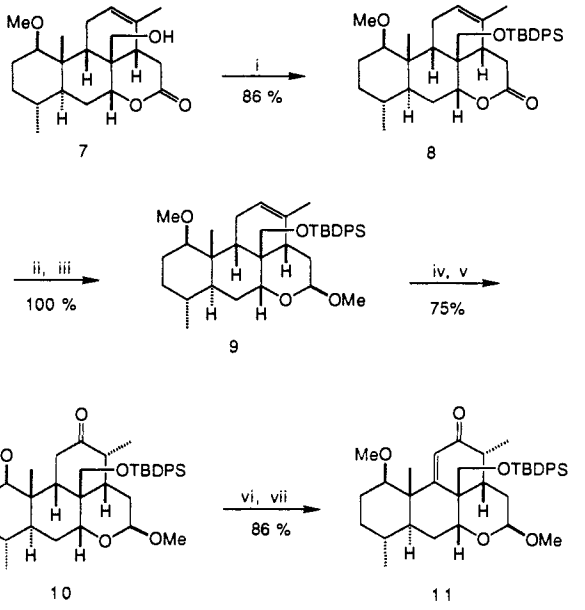
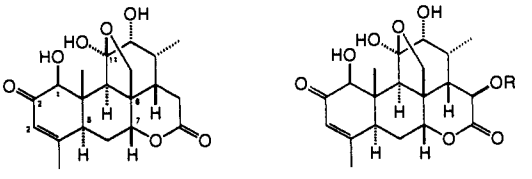
The C(8), C(11) bridged hemiketal structural array and the ring-A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit bearing a methyl group at C(4) found in chaparrinone (**1**) are structural features common to a large number of quassinoids.[1] These structural fragments appear to be essential for the rich array of pharmacological properties associated with quassinoids.[2] To date all efforts to prepare chaparrinone (**1**) and related quassinoids [cf. glaucarubinone (**2**)] have met with no success, in part, due to the incompatibility of the methods that have been developed independently for construction of the ring-A functionality[3] and the ring-C hemiketal array.[4] We detail herein the first total synthesis of (±)-chaparrinone featuring a new protocol for the elaboration of ring A which is compatible with functionality present in ring C.

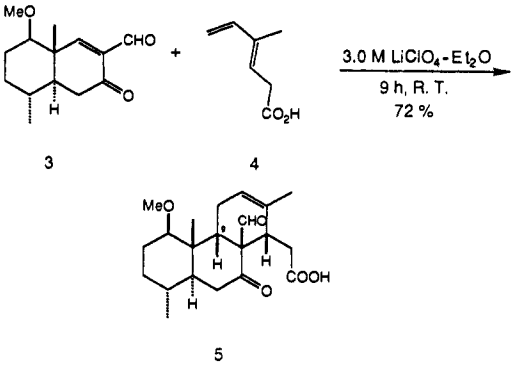
Scheme I. Preparation of Tetracyclic Enone **11**[a]



[a] (i) TBDPSCl, imidazole, DMF; (ii) *i*-Bu_2AlH, THF, −78 °C; (iii) MeOH, concentrated HCl, THF; (iv) B_2H_6, THF, 0 °C; 3 N NaOH, 30% H_2O_2; (v) PCC, NaOAc, CH_2Cl_2; (vi) LDA, THF, −78 °C → 0 °C; TMSCl, −78 °C; (vii) $Pd(OAc)_2$, Na_2CO_3, CH_3CN, 45 °C.



Our strategy for constructing the ABC carbocyclic ring system of **1** was based on a Diels–Alder approach which necessitates, at some point in the synthesis, the inversion of configuration at C(9) (cf. structure **5**). Toward this end, exposure (9 h) of dienophile



3[5] to 5.0 equiv of dienoic acid **4** in 3.0 M $LiClO_4$–diethyl ether[6] at ambient temperature gave rise in 72% yield to crystalline keto acid **5**, mp 161.5–163.0 °C. Attempts to carry out the [4 + 2] cycloaddition in refluxing toluene required 2 days and gave rise to only a 20% yield of **5**, with the major product (60%) being the

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(2) Polonsky, J. Chemistry and Biological Activity of the Quassinoids. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grundon, M. F., Eds.; Academic Press: New York, 1983; p 247.

(3) For previous reports detailing methods for the elaboration of the ring-A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality, see: Spohn, R.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491. McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897. Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568. Kim, M.; Applegate, L. A.; Pack, O.; Vasudevar, S.; Watt, D. S. *Synth. Commun.* **1990**, *20*, 989.

(4) For a report on the construction of the C(8), C(11) bridged hemiketal unit in a model system, see: Grieco, P. A.; Parker, D. T.; Garner, P.; Sasaki, S. *Tetrahedron Lett.* **1989**, *30*, 3401.

(5) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897.

(6) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

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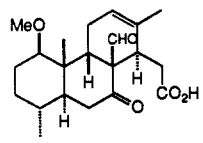
C(14) isomeric keto acid **6**. Reduction of keto acid **5** with sodium



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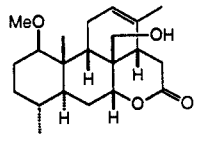
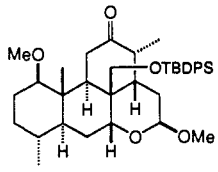
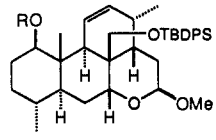


7

borohydride in methanol at 0 °C followed by treatment with concentrated hydrochloric acid afforded the crystalline tetracyclic alcohol **7**, mp 154–155 °C. To set the stage for the inversion of configuration at C(9), tetracyclic alcohol **7** was transformed into tetracyclic enone **11**, mp 178–179 °C, via tetracyclic ketone **10**, mp 190.0–191.5 °C, which was readily available by a five-step sequence from **7** (Scheme I). Conversion of **10** into its corresponding $\Delta^{11,12}$ silyl enol ether followed by treatment with palladium acetate provided the crucial enone **11**. Reduction of enone **11** in liquid ammonia at −78 °C with 10 equiv of lithium metal in the presence of 0.95 equiv of *tert*-butyl alcohol gave rise in 81% yield to tetracyclic ketone **12**, mp 162–164 °C, possessing the desired α orientation of the hydrogen atom at C(9). Function-



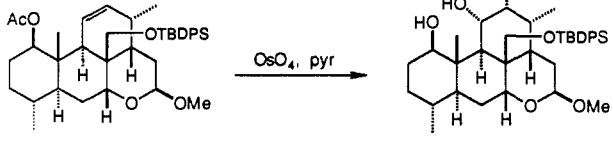
12



13

alization of the C(11) position in **12** could not be achieved directly through the agency of the corresponding enolate. Hence **12** was transformed, in 70% overall yield, into tetracyclic olefin **13** (R = Me), mp 142–144 °C, by conversion ($TsNHNH_2$, MeOH, THF) of **12** into the corresponding tosylhydrazone followed by treatment with excess *n*-butyllithium at −78 °C.

Prior to elaboration of the C(8), C(11) bridged hemiketal structural moiety found in ring C, the C(1) methyl ether was cleaved. Unfortunately the preparation of tetracyclic alcohol **13** (R = H) was complicated and necessitated a four-step sequence [(1) Jones (0 °C → room temperature); (2) BF_3·Et_2O, ethanedithiol; (3) *i*-Bu_2AlH, THF, −78 °C; (4) MeOH, PPTS] giving rise to **13** (R = H), mp 214–216 °C, in 56% overall yield. With compound **13** (R = H) in hand it was subjected to acetylation (Ac_2O, Et_3N, DMAP, CH_2Cl_2), which afforded **14** in essentially quantitative yield. Subsequent exposure of **14** to osmium tet-

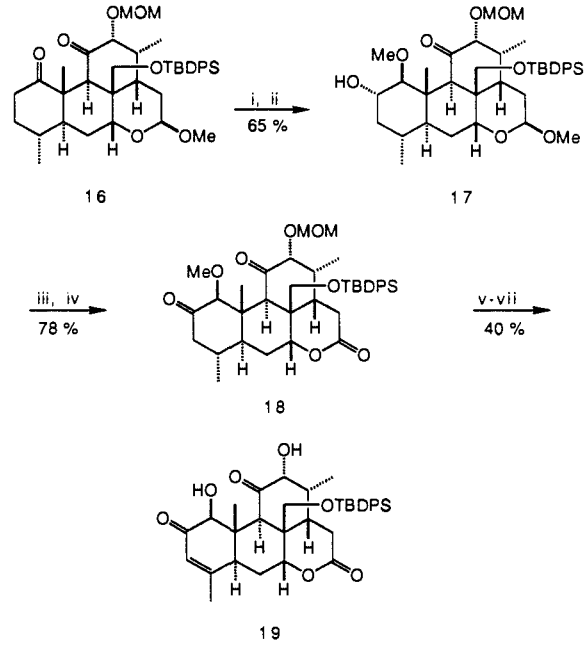


14 15

raoxide provided (83%) **15**, mp 202–205 °C, in which the acetyl group of the C(1) acetate migrated exclusively to the C(12) position as evidenced by the presence of a one-proton triplet at δ 5.18 with J = 3.1 Hz. Simultaneous oxidation (Collins reagent) of the hydroxyl groups at C(1) and C(11) of **15** followed by hydrolysis (NaOH, MeOH, THF) of the C(12) acetate and reprotection (MOMCl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$) as a methoxymethyl ether generated tetracyclic diketone **16**, mp 187.5–188.0 °C, in 70% overall yield.

With the oxidation state of ring C in place for eventual elaboration of the C(8), C(11) bridged hemiketal moiety, attention was now focused on construction of the ring-A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit. Unfortunately all previous protocols for formation of ring A were not compatible with the existing ring-C functionality. However, success was finally realized in the sev-

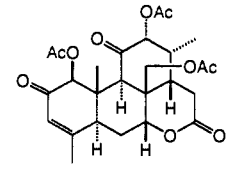
Scheme II. Elaboration of the Ring-A 1β-Hydroxy-2-oxo-$\Delta^{3,4}$ Olefin Unit[a]



16 17 18 19

[a] (i) LiHMDS, THF, HMPA; Me_2SO_4; (ii) B_2H_6, THF; NaOH, H_2O_2; (iii) HCl, H_2O, THF; (iv) PCC, NaOAc, CH_2Cl_2; (v) $PyHBr_3$ CSA, THF, 1 h; (vi) LiBr, Li_2CO_3, DMF, 120 °C, 1 h; (vii) BBr_3 (16 equiv), CH_2Cl_2 −78 °C → −23 °C, 1.5 h.

en-step sequence illustrated in Scheme II. Selective methyl enol ether formation at C(1) and subsequent hydroboration gave rise to keto alcohol **17**, whose ^1H NMR spectrum revealed the C(1) proton as a doublet at δ 2.68 with J = 9.4 Hz. Hydrolysis of the protected lactol and simultaneous oxidation at C(2) and C(16) generated tetracyclic diketo lactone **18**, mp 211.0–213.5 °C. Introduction of the $\Delta^{3,4}$ olefin into **18** followed by boron tribromide induced cleavage of the methyl ether and the MOM ether provided pre-chaparrinone **19**, mp 157–159 °C. Exposure of pre-chaparrinone **19** to tetra-*n*-butylammonium fluoride in tetrahydrofuran for 30 min provided crystalline racemic chaparrinone (**1**), mp 231–234 °C, whose spectral data (^1H NMR, IR) were in agreement with the limited ^1H NMR data in the literature.[7] The structure of **1** was confirmed by conversion (Ac_2O, pyr, DMAP) into triacetate **20**, mp 249.0–250.5 °C, whose spectral properties (IR, ^1H NMR) were identical with those recorded in the literature for a sample of **20** derived from natural chaparrinone.[7] Additional proof for the structure of **1** was established by single-crystal X-ray analysis.[8]



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(7) Polonsky, J.; Bourguignon-Zylber, N. *Bull. Soc. Chim. Fr.* **1965**, 2793.
(8) All new crystalline compounds have been fully characterized by IR, ^1H NMR, and combustion analysis.